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A3

(54) Title: **NITRIC OXIDE RELEASING PYRUVATE COMPOUNDS, COMPOSITIONS AND METHODS OF USE**

(57) Abstract: The invention describes novel pyruvate compounds comprising at least one nitric oxide releasing group and pharmaceutically acceptable salts thereof, and novel compositions comprising at least one pyruvate compound comprising at least one nitric oxide releasing group, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides novel compositions comprising at least one pyruvate compound and at least one nitric oxide donor compound and/or at least one therapeutic agent. The invention also provides novel kits comprising at least one pyruvate compound, that is optionally substituted with at least one nitric oxide releasing group, and, optionally, at least one nitric oxide donor and/or at least one therapeutic agent. The invention also provides methods for (a) treating cardiovascular diseases; (b) treating renovascular diseases; (c) treating diabetes; (d) treating diseases resulting from oxidative stress; (e) treating endothelial dysfunctions; (f) treating diseases caused by endothelial dysfunctions; (g) treating cirrhosis; (h) treating pre-eclampsia; (j) treating osteoporosis; (k) treating nephropathy; (l) reperfusion injury following ischemia; and/or (m) preserving tissues, organs, organ parts and/or limbs. The nitric oxide releasing group is preferably a nitro group (i.e. NO₂), a nitroso group (i.e. NO) and/or a heterocyclic nitric oxide donor group. The heterocyclic nitric oxide donor group is preferably a furoxan, a sydnonimine, an oxatriazole-5-one and/or an oxatriazole-5-imine.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C07D 211/38, 46; C07C 233/05 US CL : 546/242; 564/199 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 546/242; 564/199 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Please See Continuation Sheet Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LOPATIN, W., et al., Pyruvamide. 3. Involvement of the Amide Group in Carbinolamine Formation, gem-Diamine Formation, and Transimination, J. Amer. Chem. Soc., vol. 101(4), pages 960-969 (14 February 1979), especially at p. 962, col. 1, lines 1 - 7 (compounds Id and Ie) and page 963 (Table I, m- and p-nitropyruvanilide).	20
A	US 2002/0042377 A1 (STEINER, et al.) 11 April 2002 (11.04.2002), p. 29, line 22 (Example 68).	20
A	HANSON, S.R., et al., Nitric Oxide Donors: A Continuing Opportunity in Drug Design, published in Nitric Oxide: Biochemistry, Molecular Biology, and Therapeutic Implications, edited by L. Ignarro and F. Murad, Academic Press (1995), pages 383-398, especially at page 384, lines 5-20, and Figure I.	20
A	BAUER, J.A., et al., Nitric Oxide Donors: Biochemical Pharmacology and Therapeutics, published in Nitric Oxide: Biochemistry, Molecular Biology, and Therapeutic Implications, edited by L. Ignarro and F. Murad, Academic Press (1995), pages 361-381, especially at page 363 (Table I), page 367, line 17 (Organic Nitrites), p. 368, line 14 (Sydnominines), and p. 368, line 25 (S-Nitrosothiols).	20
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-8300		Authorized officer Anthony J. Paviglianiti Telephone No. (571) 272-3107

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 2004/0024057 A1 (EARL et al.) 5 February 2004 (05.02.2004), page 63, line 9 (compound 49); p. 63, line 3 (compound 32); and p. 62, line 6 (compound 26).	20
A	US 2002/0165406 A1 (EKWURIBE et al.) 7 November 2002 (07.11.2002), especially page 8, line 19 (Formula III) where R1 is methyl and R3 is nitro group.	20
A	IGNARRO, L.J., et al., Nitric Oxide Donors and Cardiovascular Agents Modulating the Bioactivity of Nitric Oxide, Circulation Research, January 11, 2002, vol. 90, pages 21-28, especially page 22, col. 1, line 11 et seq. (Direct Donors), p. 22, col. 2, line 21 et seq. (Donors Requiring Metabolism) and p. 23, col. 2, line 36 et seq. (Bifunctional Donors).	20

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1 - 19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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Continuation of Box II Reason 2:

The numerous variables, e.g., R1, Z, T3, R2, Re, Rf, A, K, K', aa, U3, D, Rb, Rc, V3, R82, Wa, Eb, p1, Ec, x, Wd, y, Wi, Ej, Wg, z, bb, h, Y3, T, Rj, Rk, o, q1, k, M1, Rm, and Rn, and their voluminous, complex meanings and their virtual incomprehensible permutations and combinations make it impossible to determine the full scope and complete meaning of the claimed subject matter. In addition, the proviso (as in Claim 4) that compounds must contain "as least one nitric oxide releasing group" encompasses a great structural diversity of compounds used to generate nitric oxide. See Hanson reference at p. 384, lines 14 - 20. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT Article 6. Thus it is impossible to carry out a meaningful search on these claims. A search will be carried out on the first discernable invention, which is the first compound of claim 20, and related compounds in Claim 20.

Continuation of B. FIELDS SEARCHED Item 2:

(periodical) Nitric oxide: Official Journal of the Nitric Oxide Society, Academic Press, vols. 1 - 12 (1997 - 2005); (book) Nitric Oxide: Biochemistry, Molecular Biology, and Therapeutic Implications, editors Louis J. Ignarro and Ferid Murad, Academic Press (1995).

Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE - STN Structure search and text search; PUBMED - text search; search terms pyruvate, oxopropanoate, oxopropanamide, oxadiazole, dicarbonyl, nitrooxy, nitrate, nitrite